REMARKS

I. Status of Claims

Upon entry of this amendment, claims 1-4, 6, 8-21, 23-24, 32-39, and 43-48 are pending in the application. Claims 32-39 have been withdrawn. Claims 12-14 have been amended. Claims 46 to 48 have been added. Claims 5, 7, 22, 25-31 and 40-42 are canceled.

Support for new claims 47 to 49 is found in originally filed claims 5 and 25.

Cancellation of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the subject matter of the canceled claims.

II. Rejection under 35 U.S.C. § 103(a)

Claims 1-4, 6, 8-21, 23, 24 and 43-45 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Classen et al ("Classen") and Garcon et al. ("Garcon") in view of the Krieg et al ("Krieg") and Schwartz et al. ("Schwartz"). In particular the Office Action alleges:

> In view of the combined teachings of Claassen et al., Garcon et al, Krieg et al and Schwartz et al it would have been obvious to a person of ordinary skill in the art to prepare a composition that comprises a Neisseria antigen, CG oligonucleotide and emulsion and optionally another adjuvant.
>
> The prior art teaches that the Neisseria antigen can be Neisseria meningitidis, Neisseria gonorrhoeae an antigen from Neisseria meningititis serogroup B (Claassen et al and Garcon et al).
>
> An adjuvant composition comprising an oligonucleotide comprising at least one CG motif and an emulsion are taught in Kreig et al, Schwartz et al and Garcon et al. Krieg et al teaches the claimed oligonucleotides as set forth in SEQ ID NO: 1 and teaches that it is a strong immune activating sequence and is a superb adjuvant.

> Krieg et al., Schwartz et al and Garcon et al teach the use of multiple adjuvants and/or immunostimulants in the compositions. Schwartz et al teaches that the specifically claimed additional adjuvants can be used in the compositions to enhance the immunomodulatory activity.
>
> The claimed invention is prima facie obvious in view of the combination of teachings as a whole found in Claassen et al, Garcon et al, Krieg et al and Schwartz et al, absent any convincing evidence to the contrary.

Applicants respectfully traverse the rejection and its supporting remarks.

To support an obviousness rejection under § 103, the references together must teach the elements of the invention, there must be a reason to make the claimed combination and there must be a reasonable expectation of success of the claimed combination.

The claims are directed to immunogenic compositions comprising a *Neisseria* antigen, a CpG oligonucleotide, and an emulsion comprising submicron oil droplets and an emulsifying agent. Nothing in the cited references points to the desirability of the combination of this particular antigen with these particular adjuvants. Furthermore, one of skill would not have had a reasonable expectation that such adjuvants in combination with a *Neisseria* antigen would work together much less exhibit a synergistic effect.

A. Obvious to try is not the standard for § 103

The Examiner cites to Claassen as an example of a *N. meningitidis* serogroup B antigen with an adjuvant to provide the *N. meningitidis* serogroup B antigen element of certain dependent claims. However, Claassen teach a complete vaccine that uses alum as an adjuvant. In fact as indicated in the final paragraph of Claassen, the vaccine was undergoing phase II clinical trials. If there was any significant defect in the immunogenicity that would require reformulation with different adjuvants, no one would invest in a phase II clinical trial due to the expense since the phase II clinical trial would need to be redone with the new formulation. Thus, based upon

Claassen there is on reason to omit the adjuvant taught and replace it with not one, but two additional adjuvants.

In making the rejection, the Examiner has asserted to it would be obvious to combine a *Neisseria* antigen with a CpG oligonucleotide and an emulsion comprising submicron oil droplets and an emulsifying agent without explanation of why one of skill would be motivated to combine such elements to form an immunogenic composition. The Examiner achieves this result by picking and choosing from a wide range of possible adjuvants that could be tested to come up with the claimed invention. However, the Federal Circuit in *In re O' Farrell* has made it clear that an "obvious to try" standard, which is characterized as "try[ing] each of numerous possible choices until one possibly arrive[s] at a successful result, wherein the prior art gave no indication as to which of many possible choices is likely to be successful," cannot be relied on to support an obviousness rejection.

Krieg et al. fails to guide one of skill in the art to use their CpG oligos as adjuvants for a *Neisseria* antigen, as they suggest a variety of uses for their CpG oligos including treatment of various diseases, including desensitization for allergies, asthma, as well as infections based on numerous infectious viri. Thus use of the CpG oligo as a adjuvant is just one of the many suggested uses for the CpG oligos of Krieg. Further, even if Krieg could be read by one of skill to suggest use of a CpG oligos as an adjuvant, it could not be read as teaching that CpG oligos be used as an adjuvant for a Neisseria antigen. Krieg suggests their compositions may be used to treat diseases caused by over one hundred different organisms, but without any teaching to select *Neisseria* in particular. See page 16 of the specification where Krieg lists various examples of infectious viri that could be treated using their CpG oligos: Retroviridae (e.g., human immunodeficiency viruses, such as HIV-1 (also referred to as HTLV-III, LAV or HTLVIII/LAV, or HIV-III; and other isolates, such as HIV-LP; Picornaviridae (e.g., polio viruses, hepatitis A virus; enteroviruses, human coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (e.g., strains that cause gastroenteritis); Togaviridae (e.g., equine encephalitis viruses, rubella viruses); Flaviridae (e.g., dengue viruses, encephalitis viruses, yellow fever viruses); Coronaviridae (e.g., coronaviruses); Rhabdoviridae (e.g., vesicular stornatitis viruses, rabies viruses); Filoviridae (e.g., ebola viruses); Paramyxoviridae (e.g.,

parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (e.g., influenza viruses); Bungaviridae (e.g., Hantaan viruses, bunga viruses, phleboviruses and Nairo viruses); Arena viridae (hemorrhagic fever viruses); Reoviridae (e.g., reoviruses, orbiviurses and rotaviruses); Birnaviridae; Hepadnaviridae (Hepatitis B virus); Parvoviridae (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (most adenoviruses); Herpesviridae (herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytornegalovirus (CMV), herpes viruses'); Poxviridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (e.g., African swine fever virus); and unclassified viruses (e.g., the etiological agents of Spongiform encephalopathies, the agent of delta hepatities (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1 = internally transmitted; class 2 = parenterally transmitted (i.e., Hepatitis Q; Norwalk and related viruses, and astroviruses), infectious bacteria that include: Helicobacterpyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sps (e.g. M. tuberculosis, M. avium, M. intracellulare, M kansaii, M gordonae), Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes (Group A Streptococcus), Streptococcus agalactiae (Group B Streptococcus), Streptococcus (viridans group), Streptococcusfaecalis, Streptococcus bovis, Streptococcus (anaerobic sps.), Streptococcus pneumoniae, pathogenic Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus antracis, corynebacterium diphtheriae, corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, Bacteroides sp., Fusobacterium nucleatum, Streptobacillus moniliformis, Treponeina pallidium, Treponema pertenue, Leptospira, and Actinomyces israelli; infectious fungi that include: Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Chlamydia trachomatis, Candida albicans; and other infectious organisms (i.e., protists) that include: Plasmodium falciparum and Toxoplasma gondii. Thus, since Krieg fails provide any teaching that would guide one of skill in the art to select *Neisseria* rather than any of the at least one hundred other pathogenic organisms described in the specification, the claimed invention is nonbovious.

Schwartz fails to teach one of skill to combine CpG oligos with oil-in-water emulsions. Schwartz teaches combination of ISS octanucleotide molecules, such as CpG oligos, with a variety of costimulatory molecules other than oil-in-water emulsions. Review of Schwartz *et al.* for their suggested costimulatory molecules to combine with Schwartz *et al.* ISS molecule reveals a sizable list that includes IL-1, IL-2, IL-4, IL-5, IL-6, IL-12, IFN-γ, TNF-α, "and the like" and oil-in-water emulsions, water-in oil emulsions, alum, liposomes, polystyrene microparticles, starch microparticles, polyphosphazene microparticles, polylactide/polyglycoside microparticles, squalene mixtures, muramyl peopdies, saponin derivatives, mycobacterium cell wall preparations, monophosphoryl lipid A, mycolic acid derivatives, nonionic block copolymer surfactants, Quil A, cholera toxin B subunit, ISCOMs, and Freund's adjuvant (complete and incomplete) (see page 12 and pages 15-19, as cited by the Examiner). Thus, review of only the pages cited by the Examiner produces 29 different costimulatory molecules mentioned by Schwartz *et al.*, a number of which are themselves broad classes of adjuvants, and yet the Examiner asserts that of all of these listed options, one of skill in the art would select oil-in-water. Applicants respectfully submit that Schwartz *et al.* does not teach the necessity of using a costimulatory molecule or even the desirability of such, much less the desirability of oil-in-water over the 28 other choices presented. At best, Schwartz *et al.* only suggests that it would be obvious to try combining one of twenty-nine different costimulatory molecule with an ISS.

Thus at best, these two references teach that one of skill in the art should try combining a CpG oligo with each and every of the at least 29 adjuvants in Schwartz with each of the antigens from each of the over hundred organisms suggested by Krieg for a total of greater than 2,900 different combinations. Thus, at best, the combined teachings only suggest that it would be "obvious to try" those at least 2,900 different combinations to arrive at the claimed composition.

Garcon teaches use of oil-in-water emulsions as adjuvants for a variety of the antigens. Garcon teaches the vaccine formulations of the invention can include antigens derived from HIV-1 (such as tat, nef, gp 120 or gp 160), human herpes viruses, such as gD or derivatives thereof or Immediate Early protein such as ICP27 from HSV I or HSV2, cytomegalovirus (esp Human; such as gB or derivatives thereof), Rotavirus (including live-attenuated viruses), Epstein Barr virus (such

as gp350 or derivatives thereof), Varicella Zoster Virus (such as gpI, Il and IE63), or from a hepatitis virus such as hepatitis B virus (for example Hepatitis B Surface antigen or a derivative thereof), hepatitis A virus, hepatitis C virus and hepatitis E virus, or from other viral pathogens, such as paramyxoviruses: Respiratory Syncytial virus (such as F and G proteins or derivatives thereof), parainfluenza virus, measles virus, mumps virus, human papilloma viruses (for example HPV6, 11, 16, 18, such as L I, L2, E6 or E7 antigens), flaviviruses (e.g. Yellow Fever Virus, Dengue Virus, Tick- borne encephalitis virus, Japanese Encephalitis Virus) or Influenza virus, or derived from bacterial pathogens such as Neisseria spp, including X gonorrhea and N. meningitidis (for example capsular polysaccharides and conjugates thereof, transferrin-binding proteins, lactoferrin binding proteins, PilC, adhesins); Streptococcus spp, including S. pneumoniae (for example capsular polysaccharides and conjugates thereof, PsaA, PspA, streptolysin, choline-binding proteins), S. pyogenes (for example M proteins or fragments thereof, C5A protease, lipoteichoic agalactiae, S. mutans; Haemophilus spp, including H. influenzae type B (for example pPRP and conjugates thereof), non-typeable H. influenzae (for example OMP26, high molecular, weight adhesins, P5, P6, lipoprotein D), H. ducreyi; Moraxella spp, including M catarrhalis, also known as Branhamella catarrhalis (for example high and low molecular weight adhesins and invasins); Bordetella spp, including B. pertussis (for example pertactin, pertussis toxin or derivatives thereof, filamenteous hemagglutinin, adenylate cyclase, fimbriae), B. parapertussis and B. bronchiseptica; Mycobacterium spp., including M. tuberculosis (for example ESAT6, Antigen 85A, -B or -C), M bovis, M leprae, M avium, M paratuberculosis, M smegmatis; Legionella spp, including L. pneumophila; Escherichia spp, including enterotoxic E. coli (for example colonization factors, heat-labile toxin or derivatives thereof, heat-stable toxin or derivatives thereof), enterohemorragic E. coli, enteropathogenic E. coli (for example shiga toxin-like toxin or derivatives thereof); Vibrio spp, including V cholera (for example cholera toxin or derivatives thereof); Shigella spp, including S. sonnei, S. dysenteriae, S. flexnerii, Yersinia spp, including E enterocolitica (for example a Yop protein) , Y. pestis, E pseudotuberculosis; Campylobacter spp, including C. jejuni (for example toxins, adhesins and invasins) and C. coli; Salmonella spp, including S. typhi, S. paratyphi, tP choleraesuis, S. enteritidis; Listeria spp., including L. monocytogenes; Helicobacter spp, including H pylori (for example urease, catalase, vacuolating toxin); Pseudomonas spp, including P.

aeruginosa; Staphylococcus spp., including S. aureus, S. epidermidis; Enterococcus spp., including E. Jaecalis, E. Jaecium; Clostridium spp., including C. tetani (for example tetanus toxin and derivative thereof), C. botulinum (for example botulinum toxin and derivative thereof), C. difficile (for example clostridium toxins A or B and derivatives thereof); Bacillus spp., including B. anthracis (for example botulinum toxin and derivatives thereof); Corynebacterium spp., including C diphtheriae (for example diphtheria toxin and derivatives thereof); Borrelia spp., including B. burgdorferi (for example OspA, OspC, DbpA, DbpB), B. garinii (for example OspA, OspC, DbpA, Dbp13), B. afzelii (for example OspA, OspC, DbpA, Dbp13), B. andersonii (for example OspA, OspC, DbpA, DbpB), B. hermsii; Ehrlichia spp., including E. equi and the agent of the Human Granulocytic Ehrlichiosis; Rickettsia spp, including R. rickettsii; Chlamydia spp., including C. trachomatis (for example MOMP, heparin binding proteins), C. pneumoniae (for example MOMP, heparin-binding proteins), C. psittaci; Leptospira spp.,'including L. interrogans; Treponema spp., including T pallidum (for example the rare outer membrane proteins), T. denticola, T. hyodysenteriae; or derived from parasites such as Plasmodium spp., including P. jalciparum; Toxoplasma spp., including T. gondii (for example SAG2, SAG3, 1g34); Entamoeba spp., including E histolytica; Babesia spp., including B. microti; Trypanosoma spp., including T cruzi,. Giardia spp., including G. lamblia; Leshmania spp., including L. major; Pneumocystis spp., including P. carinii; Trichomonas spp., including T vaginalis; Schisostoma spp., including S. mansoni, or derived from yeast such as Candida spp., including C. albicans; Cryptococcus spp., including C neoformans. Thus, Garcon suggests an even larger list of organisms to use with the oil-in-water adjuvant taught by Garcon. Thus, adding Garcon to the obviousness argument expands the number of options that one of skill in the art could screen through since Garcon suggest that their oil-in-water emulsions may be used as adjuvants for vaccines with antigens from numerous different organisms, but without any teaching to select *Neisseria* in particular. Thus, since Garcon *et al.* fails provide any teaching that would guide one of skill in the art to select a *Neisseria* antigen, rather than an antigen from any of the at least one hundred pathogenic organisms, the claimed invention is nonobvious.

Nothing in any of these three references teaches the desirability of this particular combination of adjuvants and antigens. As discussed above, the Federal Circuit has clearly stated that merely being "obvious to try" is not sufficient to establish that a claimed invention is obvious.

B. Reasonable Expectation of Success

Even if the references together would have guided one of skill to combine *Neisseria* antigen with a CpG oligonucleotide and an emulsion comprising submicron oil droplets and an emulsifying agent (which is denied), one of skill would not have had a reasonable expectation that such a combination would elicit an immunogenic response greater than the sum of the response to the antigen with each adjuvant individually. Combining an antigen with multiple adjuvants is not a predictable solution for generating a composition with synergistic immunogenicity. When combined together, adjuvants which work individually to enhance immunogenicity are more likely to exhibit a simple additive effect or possibly even exhibit reduced immunogenicity if they stimulate competing pathways.

The claimed invention is thus nonobvious, as none of the cited references teach the desirability of combining *Neisseria* antigen with a CpG oligo and an oil-in-water emulsion. Moreover, even if the cited references were to teach that this particular combination would be desirable out of the multitude of combinations taught in the cited references, one of skill would not have had a reasonable expectation that such a combination would work. Schwartz in fact supports this assertion of unpredictability of combining adjuvants. As showing in Figure 8 of Schwartz, addition of the CpG conjugate to the MF59 (an oil in water adjuvant) adjuvanted AgE only increased the IgG1 produced after 6 weeks two fold. By contrast, the specification of the present application shows on page 25, table 1, that CpG (unconjugated) with and CFA (an oil in water adjuvant) adjvanted *Neisserial* antigen increased the immunogenicity approximately five fold after the first dose and seven fold after the second dose even though only 20 μg of unconjugated CpG oligo was used was for this example while Schwartz used 50 μg of conjugated CpG oligo.

For at least the above reasons, the Examiner has failed to establish a *prima facie* case for obviousness. Withdrawal of the rejection is thus respectfully requested.

C. Unexpected results

Based on the above arguments alone, the invention is not obvious. However, in addition, unexpected results are provided in the application. Under MPEP § 2107.2, evidence of unexpected results can rebut a *prima facie* case for obviousness.

Applicants provide unexpected results in the Examples. In Example 5, sera from mice administered a 919-CFA-CG oligo formulation had antibody titers more than five times higher than sera from mice administered a 919-CFA formulation. The difference in response between the formulation containing both CFA (an oil-in-water emulsion) and a CpG oligo and the formulation with CFA alone provides at the very least a rough estimate of the ability of a CpG oligo to enhance immunogenicity of a *Neisseria* antigen. Unexpectedly, this difference was far greater than the response induced by any of the vaccine formulations with only a single oil-in-water emulsion adjuvant such as CFA, IFA and MF59. There is a difference of 3602 ELISA titer units between the 919-CFA-CG oligo and 919-CFA, while the ELISA titer is 876 for 919-CFA, 2443 for 919-IFA and 120 for 919-MF59. This data shows that the CpG oligos are either themselves unusually potent adjuvants for *Neisseria* antigens or that CpG oligos in combination with oil-in-water emulsions exhibit considerable synergy as adjuvants.

The potent effect of CpG oligos on antibody titer was even more pronounced after a second dose of the vaccine. The 919-CFA-CG oligo formulation induced antibody titers more than six times than that induced by 919-CFA formulation and the difference in the responses was, once again, significantly greater (at least four times) than that of any of the other vaccine formulations with a single oil-in-water-emulsion adjuvant.

Even further evidence of the potent effect of the CpG oligos is provided in Example 6, which shows that sera from mice immunized with 919-CFA-oligo formulation exhibited bactericidal activity at least 2 times higher than formulations with CFA alone.

This surprising effect of this particular combination of adjuvants when used with a *Neisserial* antigen is in stark contrast to the results obtained by Schwartz when adding ***more*** CpG oligo that was ***conjugated*** to AgE.

The synergy with oil-in-water emulsions in combination with CpG oligos with *Neisserial* antigens is unexpected in view of what is known in the art regarding the effects of combining multiple adjuvants in particular the teachings of Schwartz. Thus even if a *prima facie* case for obviousness had been successfully made by the Examiner, it is rebutted by evidence of unexpected results. Withdrawal of the rejection is thus respectfully requested.

III. Objections

Claims 5 and 25 have been objected to for being dependent on a rejected claim. These claims have been cancelled and rewritten to incorporate all limitations of the rejected claims as new claims 47 to 49. Applicants submit that these claims are now in condition for allowance.

IV. Conclusions

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.223002102200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 2, 2007

Respectfully submitted,

By_____/Patricia Tsao/_____
Patricia Tsao
Registration No.: 50,713
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105-2482
(415) 268-6642